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Predictive Clinical Factors in the Diagnosis of Gastrointestinal Kaposi's Sarcoma and Its Endoscopic Severity

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Abstract

Background: The diagnosis of gastrointestinal (GI) involvement in Kaposi's sarcoma (KS) is important to make because the need for treatment depends on the extent of the disease. Moreover, severe GI lesions can cause serious complications. Endoscopy with biopsy is an extremely useful method to diagnose GI-KS. However, determining the indications for endoscopy is difficult because KS can occur without GI symptoms or cutaneous KS. This study sought to clarify predictive clinical factors for GI-KS and its severity on endoscopy.

Methodology/Principal Findings: A total of 1,027 HIV-infected patients who underwent endoscopy were analyzed. Sexual behavior, CD4 count, HIV RNA, history of highly active antiretroviral therapy (HAART), GI symptoms, and cutaneous KS were assessed. Endoscopic severity including bulky tumor, ulceration, and number of lesions were evaluated. Thirty-three patients had GI-KS and 46 patients cutaneous KS. Among the GI-KS patients, 78.8% (26/33) had no GI symptoms and 24.2% (8/33) had no cutaneous KS. Univariate analysis identified men who have sex with men (MSM), CD4 $<$100 cells/μL, HIV RNA $\geq$10,000 copies/mL, no history of HAART, and cutaneous KS were significantly associated with GI-KS. Among these factors, cutaneous KS was closely related to GI-KS on multivariable analysis. Among patients without cutaneous KS, MSM and CD4 count $<$100 cells/μL were the only independent clinical factors related to GI-KS. Bulky tumor was significantly associated with CD4 $<$100 cells/μL and large number of lesions was significantly associated with HIV-RNA $\geq$10,000 copies/mL.

Conclusions: To diagnose GI-KS, clinical factors need to be considered before endoscopy. The presence of GI symptoms is not useful in predicting GI-KS. MSM and CD4 count $<$100 cells/μL are predictive factors among patients without cutaneous KS. Caution should be exercised especially in patients with low CD4 counts or high HIV viral loads as they are more likely to develop severe GI-KS lesions.

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Introduction

Kaposi's sarcoma (KS) is a rare type of cancer of the lymphatic and blood vessels that most commonly involves the skin [1–3]. KS is more prevalent in HIV-infected patients, especially among men who have sex with men (MSM) [2,3]. Although the rate of AIDS-related KS has decreased dramatically since the introduction of highly active antiretroviral therapy (HAART) [4–6], KS remains the most common malignancy among patients with AIDS [7].

The diagnosis of visceral involvement of KS is important to make because the need for treatment and choice of treatment depend on the extent of the disease [4–11]. The gastrointestinal (GI) tract is a common site of visceral involvement [12–16]. Endoscopy with biopsy is extremely useful for diagnosing GI-KS and is usually indicated for patients with GI symptoms and the presence of cutaneous KS [17,18]. However, GI-KS can occur without GI symptoms [19,20] and in the absence of cutaneous disease [20,21]. Moreover, few studies have investigated the clinical factors of GI-KS [19–21] and most of those have been case series or case reports without control subjects. Therefore, the indications for endoscopy to detect GI-KS in patients with HIV/AIDS, especially those without GI symptoms or cutaneous disease, have been difficult to determine.

Endoscopically, GI-KS can vary from flat maculopapular or polypoid masses to severe lesions. The latter can cause serious complications such as hemorrhage, perforation, and obstruction

and may require emergent treatment [14,22–26]. However, there are no reports to date on the predictive clinical factors for finding severe GI-KS lesions on endoscopy.

In Japan, screening endoscopy is frequently performed for the early detection of malignant or premalignant lesions, even as part of the examination for patients who are asymptomatic. In this study, we performed endoscopy in a large number of HIV-infected patients with or without GI symptoms and cutaneous involvement.

Methods

Objectives

We conducted a case-control study to identify predictive clinical factors for diagnosing GI-KS, especially among patients without GI symptoms and cutaneous disease. We also assessed macroscopic appearance in detail looking for predictors of severe GI-KS lesions on endoscopy.

Participants

We recruited 1,064 HIV-infected patients who had undergone endoscopy between 2003 and 2009 at the National Center for Global Health and Medicine (NCGM), a 900-bed hospital located in the Tokyo metropolitan area and the largest referral center for HIV/AIDS in Japan. We excluded patients who had received endoscopy for follow-up evaluation shortly after treatment for GI disease.

Ethics statement

The institutional review board at NCGM approved this study. All patients from whom clinical samples were obtained during endoscopy or biopsy had provided written informed consent prior to endoscopy. No ethical problems exist with regard to the publication of this manuscript. We used anonymized data from patient medical records.

Clinical factors

Before endoscopy, we routinely enter "purposes of the inspection" into the electronic endoscopic database. Purposes include examination for symptoms, screening for malignant or premalignant lesions, and follow up for endoscopic procedure or surgery. GI symptoms were assessed by the physician who interviewed each patient in detail. Those without GI symptoms and negative screening endoscopy were considered to be symptom-free.

CD4 cell counts were checked within 1 week of endoscopy. We categorized CD4 cell counts into four groups: $\geq$300 cells/μL; 200–299 cells/μL; 100–199 cells/μL; and <100 cells/μL. HIV-RNA viral load (VL) as determined by real-time quantitative polymerase chain reaction (PCR) was reviewed within 1 month of endoscopy. The minimum detection level was 40 copies/mL of plasma. A positive result for real-time HIV RNA was defined as $\geq$40 copies/mL. HIV-RNA VL was categorized into four groups: VL $\leq$40 copies/mL (normal range); 40<VL$\leq$10,000 copies/ml; 10,000<VL$\leq$100,000 copies/mL; and VL>100,000 copies/mL.

History of HAART was collected from medical records prior to endoscopy and was categorized into five groups according to duration of administration: without history of HAART; duration $\leq$6 months; 6 months<duration $\leq$1 year; 1 year<duration $\leq$5 years; duration >5 years.

HIV infection route was determined by the medical staff who interviewed each patient on the first visit to our hospital and classified into five categories: MSM, heterosexual, hemophiliac, injection drug user, and unknown. We defined sexual behavior as MSM or heterosexual. Patients who were not homosexual or bisexual were regarded as heterosexual.

Diagnosis of GI-KS

We performed biopsy when abnormal findings were encountered on upper or lower endoscopy. If we performed both upper and lower endoscopy in the same individual, this was defined as one case. GI-KS was suspected based on endoscopic appearance, such as the presence of submucosal nodules, polypoid nodules, or deep-red mucosa (Fig. 1A–C), as previously reported [16,19,27]. Endoscopic severity was evaluated in terms of appearance, including size, ulceration, and number of lesions. Regarding size, we defined bulky tumors (Fig. 1D) as circumferential or obstructive lesions and small tumors as all other cases [23]. Ulceration was defined endoscopically as a distinct, visible crater >5 mm in diameter with a slough base (Fig. 1E). The number of lesions was classified into two groups: large number ($\geq$10) (Fig. 1F) or small number (<10).

GI-KS was defined as the presence of proliferating spindle cells in biopsy specimens as seen on hematoxylin and eosin (HE) staining (Fig. 2A). Spindle cells were consistently positive on immunohistochemical staining for D2–40 (Fig. 2B), CD34 (Fig. 2C), and HHV-8 (Fig. 2D), as previously reported [28,29]. We assessed the presence of lesions in the esophagus, stomach, duodenum, terminal ileum, colon, and rectum. Before endoscopy, we examined all patients for cutaneous lesions of KS.

Statistical analysis

After summarizing the descriptive patient characteristics, to identify predictive clinical factors for diagnosing GI-KS, we calculated odds ratios (ORs) and 95% confidence intervals (CIs). The relationship between GI-KS and categories of CD4 cell count, HIV-RNA VL, and HAART duration were evaluated using the chi-square test for linear trends. For multivariable analysis, we used a multiple logistic regression model that included all factors showing values of $p<0.1$ on univariate analysis. Exact logistic regression was also used if the number in a cell was 0. A final model was then developed by backward selection of factors showing values of $p<0.10$.

The relationships between endoscopic severity of GI-KS and clinical factors were also evaluated using the chi-square test. Values of $p<0.10$ were considered significant. All statistical analysis was performed using Stata version 10 software (StataCorp LP, College Station, TX).

Results

Participants

Of the 1,064 potential study subjects recruited who underwent endoscopy, we excluded 37 who underwent endoscopy for follow-up evaluation shortly after treatment for GI diseases. Ultimately, the remaining 1,027 patients were selected for data analysis.

Baseline characteristics

Characteristics of the 1,027 patients with HIV are shown in Table 1. Median age was 44 years (interquartile range [IQR], 36–56 years). Patients were predominantly male (91.8%).

Routes of HIV infection included MSM (67.0%), heterosexual (17.0%), hemophilia (13.6%), drug usage (0.2%), and unknown (2.1%). Median CD4 count was 239 cells/μL (IQR, 100–406 cells/μL). Median HIV-RNA VL was <40 copies/mL (IQR, <40–33,000 copies/mL). A total of 739 patients (72.0%) had received HAART.

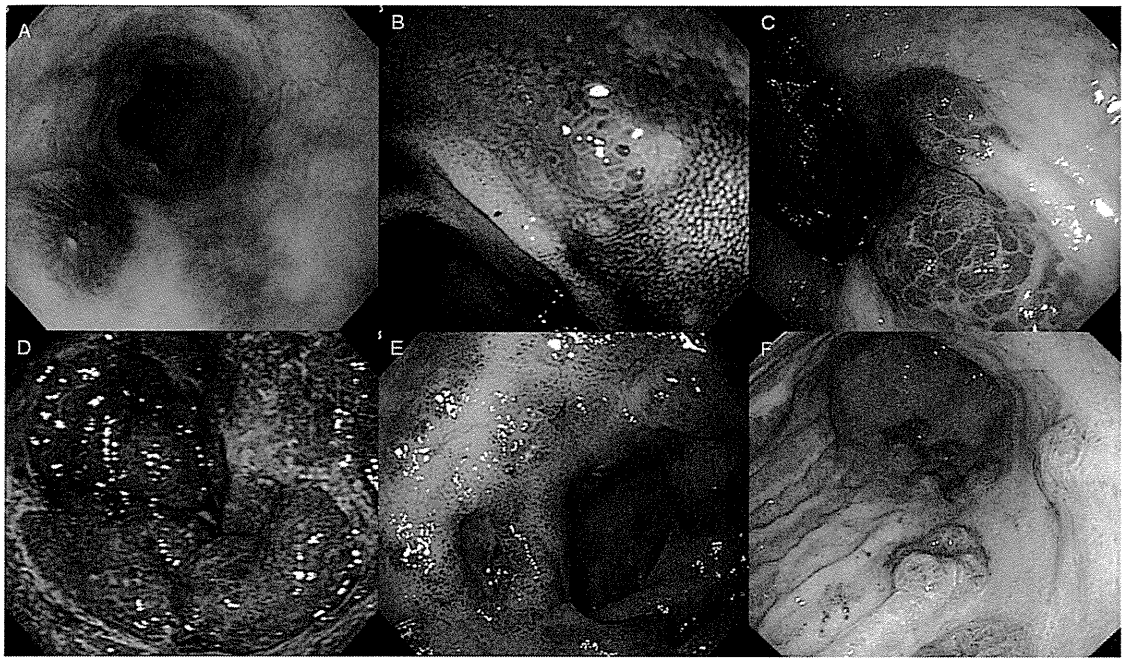

Figure 1. Gastrointestinal Kaposi's sarcoma on endoscopy. A) Dark-reddish flat lesions in the esophagus. **B**) Chromoendoscopy with indigo carmine dye showed a polypoid nodule in the terminal ileum. **C**). Submucosal lesions in the rectum. **D**) Bulky tumor surrounding the antrum of the stomach and causing pyloric stenosis. **E**) Circumferential flat lesions with ulceration in the duodenum. **F**) Multiple nodules in the stomach.
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GI symptoms were noted in 368 patients (35.8%) as follows: appetite loss (n = 6); throat pain (n = 8); dysphagia (n = 11); reflux or heartburn (n = 22); epigastric pain (n = 87); nausea or vomiting (n = 36); hematemesis (n = 25); tarry stool (n = 43); hematochezia (n = 54); diarrhea (n = 87); distended abdomen (n = 2); and lower abdominal pain (n = 17).

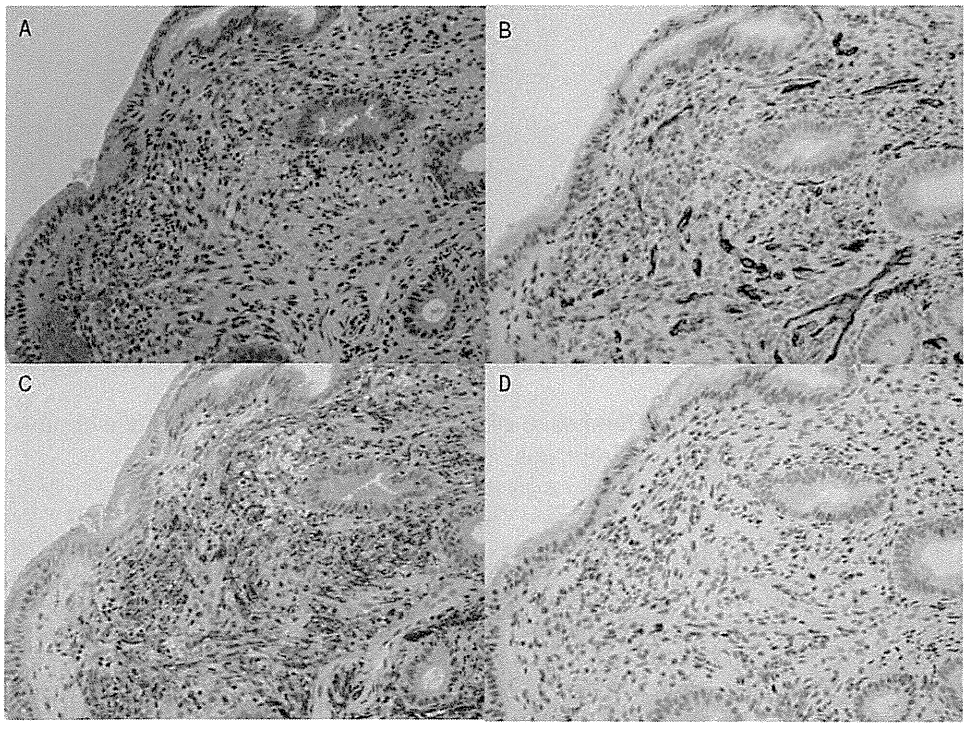

Figure 2. Pathological features of GI-KS. A) Spindle cell proliferation found in the submucosa on hematoxylin and eosin (HE) staining. **B**) Immunohistochemical staining revealing strong expression of CD34. **C**) Immunohistochemical staining revealing expression of D2–40. Vascular gaps are lined with endothelial cells on staining for CD34 and D2–40. **D**) Some endothelial cells are positive for human herpes virus 8 (HHV-8).
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Table 1. Patient characteristics.

	All (n = 1,027)	With GI-KS (n = 33)	Without GI-KS (n = 994)
Age, median (IQR)*	44 (36, 56)	44 (36, 56)	45 (35, 55)
Sex (male), n (%)	943 (91.8%)	33 (100%)	910 (91.6%)
HIV infection route, n (%)			
MSM	688 (67.0%)	31 (93.9%)	657 (66.1%)
Heterosexual	175 (17.0%)	2 (6.1%)	173 (17.4%)
Hemophiliac	140 (13.6%)	0	140 (14.1%)
Drug-user	2 (0.2%)	0	2 (0.2%)
Unknown	22 (2.2%)	0	22 (2.2%)
CD4 cell count (cells/μL)			
≥300	424 (41.3%)	1 (3.0%)	423 (42.6%)
200–299	155 (15.1%)	3 (9.1%)	152 (15.3%)
100–199	193 (18.8%)	8 (24.2%)	185 (18.6%)
<100	255 (24.8%)	21 (63.7%)	234 (23.5%)
HIV RNA (copies/mL)			
VL≤40 (normal range)	533 (51.9%)	4 (12.1%)	529 (53.2%)
40<VL≤10,000	176 (17.1%)	4 (12.1%)	172 (17.3%)
10,000<VL≤100,000	151 (14.7%)	7 (21.1%)	144 (14.5%)
VL>100,000	167 (16.3%)	18 (54.6%)	149 (15.0%)
History of HAART, n (%)			
Without history of HAART	288 (28.0%)	18 (54.6%)	270 (27.2%)
Duration ≤6 months	113 (11.0%)	8 (24.2%)	105 (10.6%)
6 months<duration≤1 yr	75 (7.3%)	7 (21.2%)	68 (6.8%)
1 yr<duration≤5 yrs	67 (6.5%)	0	67 (6.7%)
Duration >5 yrs	484 (47.1%)	0	484 (48.7%)
GI symptoms, n (%)			
Without	659 (64.2%)	26 (78.8%)	633 (63.7%)
With	368 (35.8%)	7 (21.2%)	361 (36.3%)
Cutaneous KS			
Without	981 (95.5%)	8 (24.2%)	973 (97.9%)
With	46 (4.5%)	25 (75.8%)	21 (2.1%)

Abbreviations: IQR, interquartile range; MSM, men who have sex with men; VL, viral load; yrs, years; GI, gastrointestinal.
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Characteristics of GI-KS

Of the 1,027 patients, 33 (3.2%) were diagnosed with GI-KS (Table 1). GI lesions were found in the esophagus (n = 10), stomach (n = 20), duodenum (n = 17), terminal ileum (n = 7), colon (n = 13), and rectum (n = 9). Of the patients with GI-KS, 78.8% (26/33) had no GI symptoms and 24.2% (8/33) had no cutaneous KS (Table 1).

Five of eight GI-KS patients without cutaneous involvement underwent HAART for a mean duration of 1.84 months.

Predictive clinical factors of GI-KS

Univariate analysis identified MSM, CD4 count <100 cells/μL, HIV RNA VL ≥10,000 copies/mL, no history of HAART, and the presence of cutaneous KS as significant clinical factors for the development of GI-KS (Table 2).

As the CD4 count decreased (≥300; 200–299; 100–199; and <100 cells/μL), occurrence of GI-KS increased significantly ($p<0.01$ for trend in odds, Table 1). As HIV RNA viral load increased (VL≤40; 40<VL≤10,000; 10,000<VL≤100,000; and VL>100,000 copies/ml), the occurrence of GI-KS increased significantly ($p<0.01$ for trend in odds, Table 1). Multivariable analysis showed cutaneous KS (OR, 144.8, 95%CI, 58.5–358.2, $p<0.01$) was the only independent clinical factor related to GI-KS.

Predictive clinical factors of GI-KS in patients without GI symptoms

Univariate analysis identified MSM, CD4 count <100 cells/μL, HIV RNA VL≥10,000 copies/mL, no history of HAART, and presence of cutaneous KS as significant clinical factors for the development of GI-KS (Table 2). Multivariable analysis showed cutaneous KS (OR, 128.7, 95%CI, 44.1–376.1, $p<0.01$) was the only independent clinical factor related to GI-KS.

Predictive clinical factors of GI-KS in patients without cutaneous KS

Univariate analysis identified MSM and CD4 count <100 cells/μL as significant clinical factors for the development of GI-KS (Table 2). Multivariable analysis showed MSM (OR, 5.18, 95%CI, 0.79–∞, $p = 0.09$) and CD4 count <100 cells/μL (OR,

Table 2. Predictive clinical factors for GI-KS on uni- and multivariable analysis.

	All (n = 1.027)	Without GI symptoms (n = 659)	Without cutaneous KS (n = 981)
Univariate analysis	**Odds ratio (95%CI)**	**Odds ratio (95%CI)**	**Odds ratio (95%CI)**
Age (years)			
<40	1 (referent)	1 (referent)	1 (referent)
≥40	0.84 (0.41–1.72)	1.00 (0.43–2.34)	0.54 (0.13–21.8)
Sex			
Female	1 (referent)	1 (referent)	1 (referent)
Male	4.33 (0.76–∞)†	3.70 (0.64–∞)†	1.04 (0.16–∞)†
Sexual behavior			
Heterosexual	1 (referent)	1 (referent)	1 (referent)
MSM	7.95 (1.89–33.4)*	5.67 (1.33–24.2)**	5.78 (0.89–∞)†***
CD4 cell count (cells/μL)			
≥100	1 (referent)	1 (referent)	1 (referent)
<100	5.68 (2.75–11.7)*	4.43 (1.99–9.85)*	10.3 (2.06–51.2)*
HIV RNA (copies/mL)			
<10,000	1 (referent)	1 (referent)	1 (referent)
≥10,000	7.40 (3.30–16.6)*	8.52 (3.37–21.6)*	1.49 (0.35–6.29)
History of HAART			
Without	1 (referent)	1 (referent)	1 (referent)
With	0.31 (0.15–0.63)*	0.26 (0.12–0.58)*	0.59 (0.14–2.49)
GI symptoms			
Without	1 (referent)	NA	1 (referent)
With	0.47 (0.20–1.10)***	NA	1.02 (0.24–4.30)
Cutaneous KS			
Without	1 (referent)	1 (referent)	NA
With	144.8 (58.5–358.2)*	128.7 (44.1–376.1)*	NA
Multivariable analysis	Odds ratio (95%CI)	Odds ratio (95%CI)	Odds ratio (95%CI)
MSM			5.18 (0.79–∞)†***
CD4 count <100 cells/μL			9.55 (1.69–97.7)†*
Cutaneous KS	144.8 (58.5–358.2)	128.7 (44.1–376.1)*	NA

†: Analysis by exact logistic regression.
*p<0.01.
**p<0.05.
***p<0.1.
A final model of multivariable analysis was developed by backward selection of factors showing values of p<0.05.
Abbreviations: GI-KS, gastrointestinal Kaposi's sarcoma; MSM, men who have sex with men; HAART, highly active antiretroviral therapy; NA, not applicable.
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9.55, 95%CI, 1.69–97.7, p<0.01) were the only independent clinical factors related to GI-KS.

Predictive clinical factors for endoscopic severity of GI-KS

Endoscopic severity was found in the form of bulky tumors (n = 10), ulcerous lesions (n = 11), and multiple lesions (n = 9). Relationships between endoscopic severity of GI-KS and clinical factors are shown in Table 3. In the analysis of GI-KS patients, endoscopic severity in the form of bulky tumors was found to be associated with CD4 cell count <100 cells/μL (p = 0.04). Endoscopic severity in the form of multiple lesions was found to be associated with HIV RNA VL≥10,000 copies/mL (p<0.05). No significant difference was noted in the presence of cutaneous KS between the mild groups and the severe group on endoscopy.

Discussion

Endoscopy is clearly a valuable diagnostic method for identifying GI-KS, but it is not recommended for all HIV-infected patients because of considerations of cost and invasiveness. The present study therefore sought to answer which HIV-infected patients need endoscopy to detect visceral KS.

We found that MSM, low CD4 (<100 cells/μL), high HIV RNA VL (>10,000 copies/mL), no history of HAART, and presence of cutaneous KS were predictive clinical factors for GI-KS on univariate analysis. Our findings are consistent with past studies on HIV-infected patients from Western countries that showed an association between clinical factors and cutaneous KS or visceral KS [2,2,4–7,9–13].

Endoscopy is usually considered to be indicated for GI-KS diagnosis in patients who have GI symptoms [17,18]. However,

Table 3. Relationship between endoscopic severity of GI-KS and clinical factors (n = 33).

Factor	GI-KS with small tumor (n = 23)	GI-KS with bulky tumor (n = 10)	GI-KS without ulcer (n = 22)	GI-KS with ulcer (n = 11)	GI-KS small number (n = 24)	GI-KS large number (n = 9)
Age (yrs) ≥40	60.9%	60.0%	68.2%	45.5%	58.3%	66.7%
Sex (male)	100%	100%	100%	100%	100%	100%
Sexual behavior (MSM)	91.3%†	100%†	95.5%‖	90.9%‖	95.8%¶	88.9%¶
CD4 cell counts <100 cells/μL	52.2%†	90.0%†	59.1%‖	72.2%‖	62.5%¶	66.7%¶
HIV RNA ≥10,000 copies/mL	73.9%†	80.0%†	68.2%‖	90.9%‖	66.7%¶	100%¶
History of HAART	47.8%†	40.0%†	45.5%‖	45.5%‖	45.8%¶	44.4%¶
With GI symptoms	21.7%	20.0%	22.7%	18.2%	25.0%	11.1%
With cutaneous KS	21.7%†	30.0%†	77.3%‖	72.7%‖	79.2%¶	66.7%¶

†: Analysis by chi-square test between GI-KS with small tumor and bulky tumor, MSM (p = 0.34), CD4 (p<0.05), HIV-RNA (p = 0.71), history of HAART (p = 0.68), and presence of cutaneous KS (p = 0.61).
‖: Analysis by chi-square test between GI-KS with small tumor and bulky tumor, MSM (p = 0.61), CD4 (p = 0.44), HIV-RNA (p = 0.15), history of HAART (p = 1.00), and the presence of cutaneous KS (p = 0.77).
¶: Analysis by chi-square test between GI-KS with small tumor and bulky tumor, MSM (p = 0.61), CD4 (p = 0.83), HIV RNA (p<0.05), history of HAART (p = 0.94), and presence of cutaneous KS (p = 0.46).
Abbreviations: GI-KS, gastrointestinal Kaposi's sarcoma; MSM, men who have sex with men; HAART, highly active antiretroviral therapy.
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GI-KS can reportedly be detected even in patients without GI symptoms [19,20]. Indeed, we found that 79% of the patients we identified with GI-KS were asymptomatic. Both uni- and multivariable analysis showed that the presence of GI symptoms is not useful in predicting GI-KS. Furthermore, predictive factors for GI-KS were unchanged among patients without GI symptoms.

Previous studies have shown that KS occurs more commonly among MSM with AIDS than among heterosexual individuals with AIDS [2,7,8]. However, the true sexual behavior of a patient might not be able to be ascertainable in interviews, as was attempted in this study. Some MSM patients may well have been included among the unknown cases of non-GI-KS patients, in whom the OR of sexual behavior would be difficult to evaluate.

HAART is known to represent a highly effective treatment for GI-KS, and can improve the immune status of patients [4–6,9–11]. The present study found that a history of long-term administration of HAART reduced the occurrence of GI-KS.

It has previously been shown that patients with KS typically have a low CD4 cell count (<150 cells/μL) and a high HIV RNA VL (>10,000 copies/mL) [9–11]. However, CD4 levels and HIV-RNA VLs have yet to be fully investigated in GI-KS patients. The present study demonstrated that the prevalence of GI-KS tended to increase significantly with low CD4 cell count and with high HIV RNA VL. The presence of GI involvement with KS may vary according to immune status.

KS manifests primarily as a cutaneous disorder, with visceral involvement considered to occur subsequently [2,12]. In this study, the presence of cutaneous KS was found to be closely related to GI-KS on uni- and multivariable analysis. These results suggest that endoscopy may be indicated for patients with cutaneous KS.

It has been reported that GI-KS can occur in the absence of cutaneous disease [20,21]. Thus, we assessed the clinical factors among patients without cutaneous disease. We found that MSM and CD4 count <100 cells/μL were the only independent clinical factors related to GI-KS. Our results represent the first confirmation of this finding evaluated in a case-control study.

We investigated the possibility that HAART administration led to the disappearance of cutaneous KS prior to the diagnosis of GI-KS in patients without cutaneous involvement. In fact, five of eight GI-KS patients without cutaneous KS had a history of HAART. However, the mean duration of the administration was less than 2 months, and it is difficult to imagine that cutaneous KS disappeared from the whole body in such a short period of time. Therefore, it is unlikely that HAART administration had any involvement in the absence of cutaneous KS in these GI-KS patients.

In this study, we assessed endoscopic severity such as tumor bulk, ulceration, and multiple lesions as these may cause obstruction, hemorrhage, and perforation [14,22–26]. We found, for the first time, that CD4 count (<100 cells/μL) or high HIV RNA VL (≥10,000 copies/mL) were key clinical factors to predict severe GI lesions on endoscopy.

A key limitation of this study was the single-center, retrospective nature of the investigation. When considering indications for endoscopy, a randomized controlled study is required to identify whether endoscopy can prevent the development of severe GI complications in HIV-infected patients, particularly among those with a low CD4 count. Second, the number of GI-KS patients was relatively small, especially those without cutaneous KS. The statistical power of the study might thus have been low due to the small number of cases.

Conclusions

To diagnose GI-KS, clinical factors need to be considered before endoscopy is undertaken. Presence of GI symptoms is not useful in predicting GI-KS. The presence of cutaneous KS, MSM sexual behavior, low CD4 count (<100 cells/μL), high HIV RNA VL, and no history of HAART are predictive factors for GI-KS. Even if patients have no cutaneous KS, endoscopy may be suitable for patients with MSM and low CD4 count (<100 cells/μL). Caution should be exercised especially in patients with a low CD4 count (<100 cells/μL) or high HIV RNA VL (≥10,000 copies/mL) as they are more likely to develop severe GI-KS lesions. This diagnostic strategy could facilitate early diagnosis of GI-KS.

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Author Contributions

Conceived and designed the experiments: NN SO NU. Performed the experiments: NN TI. Analyzed the data: KT NO TS. Contributed reagents/materials/analysis tools: HY NA. Wrote the paper: NN SO NU JA KT NO.

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Clinical Study

False-Negative Results of Endoscopic Biopsy in the Diagnosis of Gastrointestinal Kaposi's Sarcoma in HIV-Infected Patients

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Kaposi's sarcoma (KS) is a rare endothelial neoplasm mainly involving the skin, but it is often associated with AIDS. Diagnosis of gastrointestinal (GI) tract KS, a common site of visceral involvement in AIDS, is important, but endoscopic biopsy carries a risk of false-negative results (FNRs) due to its submucosal appearance. This study sought to determine the rate and causes of FNR for endoscopic biopsy of GI-KS lesions. Endoscopic biopsy samples of 116 GI-KS lesions were reviewed retrospectively. All GI-KS lesions were confirmed to be resolved following KS therapy. FNRs were yielded for 41 of the lesions (35.3%). Among upper and lower GI sites, the esophagus was the only site significantly associated with FNRs ($P < 0.01$). Small size (<10 mm) and patches found on endoscopy were significantly associated with FNRs ($P < 0.05$). Findings of submucosal tumor (SMT) with ulceration were significantly associated with true-positive results ($P < 0.05$). In conclusion, FNRs were found in 35.3% of GI-KS lesions and were especially related to the site of the esophagus and endoscopic early stage (small size or patch appearance). An SMT with ulceration may be relatively easy to diagnose on endoscopic biopsy. Caution should be exercised when performing endoscopic biopsy of these lesions in AIDS patients and evaluating the histological features.

1. Introduction

Kaposi's sarcoma (KS) is a cancer of the lymphatic and blood vessels that mainly involves the skin [1–3]. It is a rare cancer but has become more widely known as one of the AIDS-defining illnesses [2, 3]. Although the rate of AIDS-related KS has decreased dramatically since the introduction of highly active antiretroviral therapy (HAART) [4–6], KS remains the most common malignancy among patients with AIDS [7].

KS can also involve the oral cavity, lymph nodes, and viscera [1–3, 8]. The diagnosis of visceral KS is important because the need for treatment and choosing among the various options depend upon the extent of disease [8–10]. The gastrointestinal (GI) tract is a common site of visceral involvement [11–15], and a definitive diagnosis of GI-KS can be made by endoscopic tissue biopsy [8, 16, 17]. Histopathologically, GI-KS is characterized by spindle cells that form vascular channels, which fill with blood cells [17, 18]. Endoscopically, GI-KS has various macroscopic presentations: patches, polypoid lesions, submucosal nodules, bulky masses, and ulcerations [13, 17, 19–23]. For submucosal nodules especially, endoscopic biopsy sampling

has been known to yield false-negative results (FNRs) [17, 23–25]. Some GI-KS lesions might be more difficult to identify histologically depending on their location, size, or macroscopic appearance; however, which findings are related with false-negative histological results remain unknown.

The purpose of this study was to determine the rate and causes of FNR from endoscopic biopsies of GI-KS lesions.

2. Materials and Methods

2.1. Subjects. Histopathology slides of endoscopic biopsy samples of 116 consecutive, GI-KS lesions from 24 HIV-infected patients who had not received anti-KS therapy were retrospectively reviewed. All biopsies were performed between 2002 and 2006 at the National Center for Global Health and Medicine (NCGM), a 900-bed hospital located in the Tokyo metropolitan area with the largest referral center for HIV/AIDS in Japan.

2.2. Ethics Statement. The institutional review board at NCGM approved this study. All patients from whom clinical samples were obtained during endoscopic biopsy provided written informed consent prior to the procedure. Data obtained from the patient medical records was anonymized before analysis.

2.3. Clinical Factors. HIV infection route was determined by the medical staff who interviewed each patient on the first visit to our hospital. Routes of HIV infection were determined by medical staff who questioned each patient face to face on the first visit to our hospital. Routes were classified into six categories: homosexual, bisexual, heterosexual, drug user, untreated blood products, and unknown. Patients who were homosexual or bisexual were regarded as men who have sex with men (MSM).

$CD4^+$ cell counts were checked within 1 week of endoscopy. HIV-RNA viral loads (VLs) determined by real-time quantitative polymerase chain reaction (PCR) were reviewed within 1 month of endoscopy. The minimum detection level was 40 copies/mL of plasma. A positive result for real-time HIV-RNA was defined as ≥40 copies/mL.

2.4. Diagnosis of GI-KS. Biopsy was performed using biopsy forceps (FB-240U, FB230-K; Olympus Co., Tokyo, Japan). All biopsies were performed by well-trained endoscopists (experience of >1.000 colonoscopies).

A definitive diagnosis of GI-KS was defined as follows.

(1) Negative results confirmed from biopsy samples for other GI diseases such as infection, inflammatory bowel disease, hyperplastic polyp, fundic gland polyp, inflammatory polyp, adenomatous polyp, angioectasia, GI lymphoma, premalignant lesion, esophageal cancer, gastric cancer, and colorectal cancer.

(2) Presence of proliferating spindle cells (Figure 1) with vascular channel formations filled with blood cells (Figure 1) seen on hematoxylin and eosin (HE) staining. Lesions with the absence of these findings from biopsy samples were defined as FNR.

(3) Positive response to KS therapy (HAART or systemic therapy of liposomal anthracycline); in particular, for visible GI-KS lesions without typical pathological findings from biopsy specimens, partial or complete resolution confirmed on follow-up endoscopy following KS therapy.

Table 1: Baseline characteristics of GI-KS patients ($N = 24$).

Age, years (IQR)	39 (34.5–49.5)
Sex, male (%)	24 (100)
MSM	24 (100)
CD4 cell counts, cells/mL (IQR)	71 (15.5, 177.5)
HIV viral load, copies/mL (IQR)	115,000 (2,900, 145,000)
GI symptoms (%)	8 (33.3%)

IQR: interquartile range; GI: gastrointestinal; MSM: men who have sex with men.

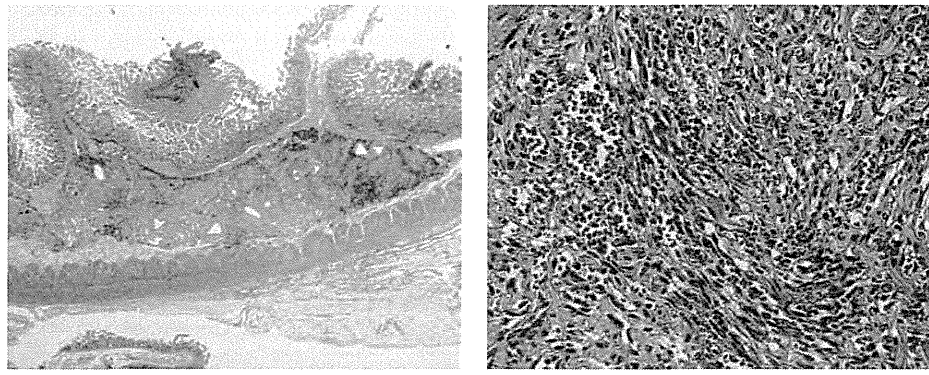
2.5. Endoscopic Assessment of GI-KS. GI-KS was evaluated in terms of site, size (≤10 mm or >10 mm), and macroscopic findings on endoscopy. Site of GI involvement was classified into 7 regions: esophagus, stomach, duodenum, ileum, right-side colon (cecum, ascending colon, and transverse colon), left-side colon (descending colon and sigmoid colon), and rectum. Macroscopic findings were evaluated in the presence of reddish mucosa with patches (Figure 2(a)), polypoid lesion (Figure 2(b)), submucosal tumor (SMT), SMT with ulceration (Figure 2(c)), and bulky mass (Figure 2(d)), as previously reported [13, 17, 19–23]. Ulceration was defined endoscopically as a distinct, visible crater >5 mm in diameter with a slough base.

2.6. Statistical Analysis. The descriptive patient characteristics were summarized, and the absence rate of spindle cells or vascular formations on pathology for the 116 samples was then analyzed to elucidate the FNR rate of endoscopic biopsy. To determine the cause of FNRs, the relationships between FNR and endoscopic findings (size, site, macroscopic appearance) were evaluated using the χ^2 test. Those factors that emerged as significant ($P < 0.10$) on univariate analysis were included in a multiple exact logistic regression model. A final model was then developed by backward selection of factors showing values of $P < 0.10$ and odds ratios (ORs) and 95% confidence intervals (CIs) estimated.

Values of $P < 0.10$ were considered significant. All statistical analyses were performed using Stata version 10 software (StataCorp LP, College Station, TX, USA).

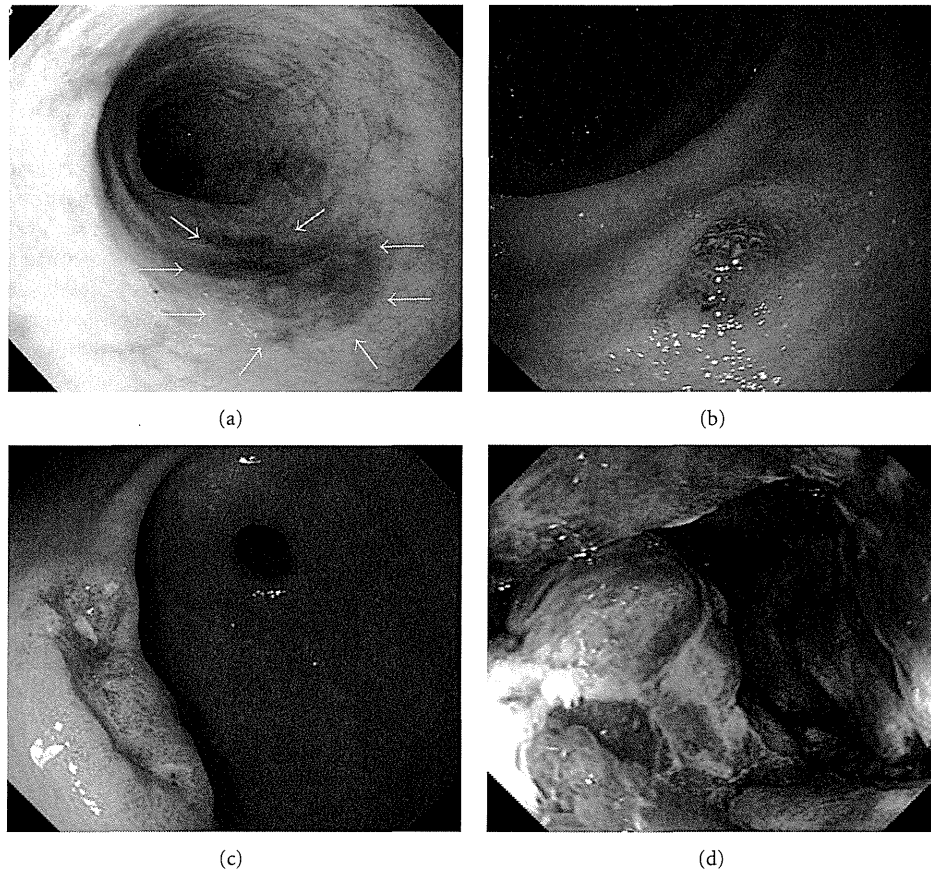
3. Results

3.1. Baseline Characteristics. Characteristics of the 24 patients are shown in Table 1. All patients were males (100%) and the HIV infection route was MSM in all cases. Median $CD4^+$ count was 71 cells/mL and median HIV-RNA VL was



(a) (b)

FIGURE 1: Pathological features of GI-KS on HE staining. (a) Low-power view showing a distinct proliferative lesion within the submucosa of the small bowel intestine. (b) High-power view showing spindle cell proliferation with vascular channel formations filled with blood cells.



(a) (b)

(c) (d)

FIGURE 2: Gastrointestinal Kaposi's sarcoma on endoscopy. (a) Dark reddish patch lesion (arrow) in the esophagus. (b) Small (≤10 mm) and polypoid lesion in the duodenum. (c) Submucosal tumor-like lesion with ulceration in the stomach. (d) Bulky tumor mass surrounding the anorectal area causing anorectal stenosis.

115,000 copies/mL. GI symptoms were noted in 8 patients (33.3%) as follows: epigastric pain ($n = 4$), nausea or vomiting ($n = 3$), hematemesis ($n = 1$), melena ($n = 1$), hematochezia ($n = 2$), and diarrhea ($n = 2$) (duplicate data).

3.2. Macroscopic Appearance of GI-KS on Endoscopy. A total of 113 GI-KS lesions were from 24 HIV-infected patients (Table 2). "Patches" appearance was noted in 40 lesions (34.5%) which were located mainly in the duodenum ($n = 8$, 20.0%) and right-side colon ($n = 9$, 22.5%). Only one lesion with "Polypoid" appearance was noted in the terminal ileum. "SMT" appearance was noted in 46 lesions (39.7%) located mainly in the stomach ($n = 18$, 39.1%) and duodenum ($n = 14$, 30.4%). "SMT with ulcer" appearance was noted in

Table 2: Macroscopic appearances of GI-KS on endoscopy according to the GI site ($n = 116$).

GI site	Patches ($n = 40$)	Polypoid ($n = 1$)	SMT ($n = 46$)	SMT with ulcer ($n = 26$)	Bulky tumor ($n = 3$)
Upper GI	15 (37.5%)	0	33 (71.7%)	19 (73.1%)	0
Esophagus	3 (7.5%)	0	1 (2.2%)	0	0
Stomach	4 (10.0%)	0	18 (39.1%)	10 (38.5%)	0
Duodenum	8 (20.0%)	0	14 (30.4%)	9 (34.6%)	0
Lower GI	25 (62.5%)	1 (100%)	13 (28.3%)	7 (26.9%)	3 (100%)
Ileum	5 (12.5%)	1 (100%)	0	0	0
Right-side colon	9 (22.5%)	0	6 (13.0%)	5 (19.2%)	0
Left-side colon	5 (12.5%)	0	6 (13.0%)	1 (3.9%)	0
Rectum	6 (15.0%)	0	1 (2.2%)	1 (3.9%)	3 (100%)

GI: gastrointestinal; SMT: submucosal tumor.

Table 3: Rate and causes of false-negative endoscopic biopsy results for GI-KS lesions on univariate analysis.

	GI-KS lesions ($n = 116$)	Lesions with true-positive results ($n = 75$)	Lesions with false-negative results ($n = 41$)	P value
Site				
Upper GI tract	67 (57.8%)	39 (68.3%)	28 (52.0%)	0.09
Esophagus	4 (3.45%)	0	4 (9.76%)	**<0.01**
Stomach	32 (27.6%)	19 (25.3%)	13 (31.7%)	0.46
Duodenum	31 (26.7%)	20 (26.7%)	11 (26.8%)	0.99
Ileum	6 (5.17%)	5 (6.67%)	1 (2.44%)	0.33
Lower GI tract	49 (42.2%)	36 (48.0%)	13 (31.7%)	0.09
Right-side colon	20 (17.2%)	15 (20.0%)	5 (12.2%)	0.29
Left-side colon	12 (10.3%)	8 (10.7%)	4 (7.32%)	0.88
Rectum	11 (9.48%)	8 (10.7%)	3 (7.32%)	0.56
Size <10 mm	23 (19.8%)	10 (13.3%)	13 (31.7%)	**<0.05**
Macroscopic appearance				
Patches	40 (34.5%)	18 (24.0%)	22 (53.7%)	**<0.01**
Polypoid lesion	1 (0.86%)	1 (1.33%)	0	0.46
SMT	46 (39.7%)	31 (41.3%)	15 (36.6%)	0.62
SMT with ulcer	26 (22.4%)	22 (29.3%)	4 (9.76%)	**<0.05**
Bulky mass	3 (2.59%)	3 (4.00%)	0	0.19

GI: gastrointestinal; SMT: submucosal tumor.

Table 4: Factors associated with false-negative endoscopic biopsy results in GI-KS lesions on multivariate analysis ($n = 116$).

	Odds ratio	95% CI	P value
Esophageal site	7.26	0.82–∞	0.08
Patches on endoscopy	3.30	1.33–8.36	<0.01

GI: gastrointestinal; CI: confidential interval.

26 lesions (22.4%) located mainly in the stomach ($n = 10$, 38.5%) and duodenum ($n = 9$, 34.6%). "Bulky tumor" appearance was noted in 3 lesions only in the rectum.

3.3. Diagnostic Yield of GI-KS on Endoscopic Biopsy. No clinical complications of GI-KS lesions were seen. There were no significant gastrointestinal bleeds or perforations, either spontaneous or after endoscopic biopsy. Diagnostic yield of GI-KS is shown in Table 3. Among the 116 lesions, 75 (64.7%) were histologically proven by endoscopic biopsy (true-positive results), while 41 (35.3%) were negative histological results (FNR) that were confirmed to have resolved following KS therapy.

Among the GI locations, the esophagus was significantly ($P < 0.01$) associated with FNR. In regards to the size of lesions, those <10 mm in diameter were significantly associated with FNR ($P < 0.05$). As for macroscopic appearance, patches were significantly associated with FNR ($P < 0.01$), while a finding of SMT with ulceration was significantly associated with true positive results ($P < 0.05$).

On multivariate analysis, the esophageal site and a patch pattern on endoscopy were independently associated with FNR (Table 4).

4. Discussion

Endoscopy is clearly a valuable diagnostic method for identifying GI-KS, but it may produce FNR. Firstly, we found

that FNR were yielded in 41 of the 116 lesions (35.3%) in this study. Previous studies on GI-KS patients have also reported a relatively low diagnostic yield for endoscopic biopsy [17, 23–25]. Friedman et al. [17] found a diagnostic yield of 23% with a potential false-negative rate of 77%, while Saltz et al. [24] reported a diagnostic yield of 15% and thus a potential false-negative rate of 85%. Moreover, in a study of non-AIDS patients by Kolios et al. [25], biopsies resulted in a definitive diagnosis in 5 of 26 patients (19.2%). However, it is important to keep in mind that the lesions that led to the FNRs in these studies might have included non-KS GI diseases. In the present study, we defined GI-KS as biopsy specimens negative for other GI diseases and with a positive response to KS therapy, such as shrinkage or disappearance of lesions, and we strictly adhered to these diagnostic criteria.

Various clinical factors can contribute to FNR on biopsy. Submucosal location or tumor growth is considered to account for the poor diagnostic yield of standard forceps biopsies [17, 23]. Moreover, it has been suggested that the size of biopsy forceps used was 5 mm in the upper GI tract or 8 mm in the lower GI tract [17]. We also used forceps similar in size in the present study. We hypothesized that in the analysis of endoscopic biopsy of GI-KS, FNR varies with site in the GI tract, lesion size, and macroscopic appearance.

Secondly, with regard to the GI site, we found the esophagus to be the only site associated with FNR on both univariate and multivariate analyses. In this study, we assessed the site by dividing the GI into 7 parts. Because it is difficult to differentiate the ascending colon from the cecum and the descending colon from the sigmoid colon on endoscopy, we divided the colon into the right-side and left-side colon. No other study has divided the GI tract into small segments and investigated the diagnostic yield in such detail as in the present study. The yield of endoscopic biopsy in the upper GI tract has been estimated as 13%, which is low compared with 36% on sigmoidoscopy [17]. It is not clear if the low diagnostic rate for the esophagus contributed to the result. The most likely explanation is that lesions in the esophagus had almost a patchy appearance, but the number of lesions at this site was relatively small ($n = 4$). Further prospective studies with a larger number of patients are needed.

Thirdly, in terms of the endoscopic appearance of GI-KS, small lesions (<10 mm) and patches were found to be significantly associated with FNR on univariate analysis. Because such characteristics could be confounding factors, we performed multivariate analysis and found that patches were correlated with FNR as an independent factor. We suggested that these lesions contain only a small amount of tumor tissue, which made such biopsy specimens too small to be diagnostically useful. On the other hand, the finding of "SMT with ulceration" was significantly associated with true-positive results, and these lesions were easily diagnosed by biopsy. This result may be attributable to the ulcerous appearance of the tumor, which makes it easy to obtain samples from the submucosal layer [26, 27].

Fourth, we found that endoscopic biopsy is a safe diagnostic method for GI-KS even in the presence of an ulcerative or bulky tumor. A previous report [19] also highlighted the importance of biopsy for distinguishing protruded lesions from KS and that biopsy for GI-KS was not associated with bleeding complications, which are consistent with the present results.

Endoscopists and clinicians should become familiar with characteristic endoscopic images of GI-KS and recognize that the diagnostic yield of GI-KS varies depending on the morphological features. In addition, pathologists should carefully evaluate lesions associated with FNR. Because KS-related GI lesions indicate visceral involvement, the indications for and selection of HAART and systemic chemotherapy need to be considered [8–10]. GI-KS often starts out as small patches in the early stage, and KS should not be ruled out just because the biopsy result is negative. It was recently reported that immunohistochemistry for human herpesvirus-8 (HHV8), CD31, CD34, and D2-40 is useful for differentiating KS from other gastrointestinal tumors of similar appearance [28]. When hematoxylin and eosin staining does not show characteristic proliferating spindle cells with vascular channel formations filled with blood cells, the application of such immunohistochemical analysis may reduce the frequency of FNR.

5. Conclusions

Endoscopic biopsy is essential for diagnosing GI-KS and it is a safe method. While FNR were found in 35.3% of lesions, FNRs differed according to a lesion site, size, and macroscopic appearance. On endoscopic biopsy, FNR was related with early-stage KS (small size or patches appearance) and site of esophagus, whereas SMT with ulceration is relatively easy to diagnose. Caution should be exercised when performing endoscopic biopsy of these lesions in AIDS patients and evaluating the histological features.

Conflict of Interests

The authors declare that they have no conflict of interests.

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Kimura et al. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine 2012, 20:9
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The development of simple survival prediction models for blunt trauma victims treated at Asian emergency centers

Akio Kimura[1*], Shinji Nakahara[2] and Witaya Chadbunchachai[3]

Abstract

Background: For real-time assessment of the probability of survival (Ps) of blunt trauma victims at emergency centers, this study aimed to establish regression models for estimating Ps using simplified coefficients.

Methods: The data of 10,210 blunt trauma patients not missing both the binary outcome data about survival and the data necessary for Ps calculation by The Trauma and Injury Severity Score (TRISS) method were extracted from the Japan Trauma Data Bank (2004-2007) and analyzed. Half (5,113) of the data was allocated to a derivation data set, with the other half (5,097) allocated to a validation data set. The data of 6,407 blunt trauma victims from the trauma registry of Khon Kaen Regional Hospital in Thailand were analyzed for validation. The logistic regression models included age, the Injury Severity Score (ISS), the Glasgow Coma Scale score (GCS), systolic blood pressure (SBP), respiratory rate (RR), and their coded values (cAGE, 0-1; cISS, 0-4; cSBP, 0-4; cGCS, 0-4; cRR, 0-4) as predictor variables. The coefficients were simplified by rounding off after the decimal point or choosing 0.5 if the coefficients varied across 0.5. The area under the receiver-operating characteristic curve (AUROCC) was calculated for each model to measure discriminant ability.

Results: A group of formulas (log (Ps/1-Ps) = logit (Ps) = -9 + cISS - cAGE + cSBP + cGCS + cRR/2, where -9 becomes -7 if the predictor variable of cRR or cISS is missing) was developed. Using these formulas, the AUROCCs were between 0.950 and 0.964. When these models were applied to the Khon Kean data, their AUROCCs were greater than 0.91. Conclusion: These equations allow physicians to perform real-time assessments of survival by easy mental calculations at Asian emergency centers, which are overcrowded with blunt injury victims of traffic accidents.

Background

The Trauma and Injury Severity Score (TRISS) [1,2] is a standard method for estimating survival and is often used to evaluate the quality of trauma care. However, it requires the Injury Severity Score (ISS) [3], the Revised Trauma Score (RTS) [4] calculated based on the Glasgow Coma Scale score (GCS), the systolic blood pressure (SBP), the respiratory rate (RR), and the categorically coded value of age (cAGE). The formulas are:

$$\text{Probability of survival (Ps)} = 1/(1 + e^{-b}),$$
$$\text{where } b = -0.4499 - 0.0835*\text{ISS} + 0.8085*\text{RTS} - 1.743*\text{cAGE} \quad [2]$$
$$\text{RTS} = 0.9368 * \text{cGCS} + 0.7326*\text{cSBP} + 0.2908*\text{cRR} \quad [4]$$

Collecting all of this information and performing such complex calculations are not feasible in the clinical setting at emergency centers. For clinicians, especially emergency physicians, it is hoped that a way to predict survival of trauma victims more easily without a significant decrease in accuracy could be developed.

This study aimed to establish regression models for quick assessment of Ps for blunt trauma (BT) victims based on simplified coefficients that could be used even when the variable of RR or the variable of ISS is missing. The former is frequently missing in the trauma registry data of Japan [5], and the latter is rarely determined during the early stage of trauma management in most cases.

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Methods

Study design, population, and settings

A retrospective observational study was conducted to create Ps prediction models with simple coefficients for BT victims in Japan and Thailand.

Once approval was obtained from the trauma registry committee of the Japanese Association for the Surgery of Trauma, deidentified, anonymous data from the Japan Trauma Data Bank (JTDB), with which 144 Japanese hospitals have been involved since 2004, were used [6].

Data (10,210) that were not missing both outcome data about survival and the predictors necessary for Ps calculation by the TRISS method were collected from BT patients (17,564) registered in the JTDB from 2004 to 2007. Half (5,113) of the data was randomly allocated to a derivation data set, with the remaining half (5,097) allocated to a validation data set.

For international validation, with the permission of the hospital, the proposed equations were applied to 6,409 of 6,667 BT patients injured in the Khon Kaen District in Thailand between January 2005 and December 2008 and collected in the Khon Kaen Regional Hospital Trauma Registry, where data have been collected since 1997. This hospital is one of the World Health Organization (WHO) collaborating centers for injury prevention and safety promotion. The data of two patients were excluded because they were erroneous.

The independent variable was survival (survival = 1; non-survival = 0). Age, the ISS, the GCS, SBP, RR, and their coded values (cAGE, cISS, cSBP, cGCS, cRR), defined in Table 1, were used as predictor variables. The GCS, SBP, RR, and age were coded according to the RTS [4] and the TRISS method [1,2]. For ISS categorization to cISS, recursive partitioning, which is an exploratory technique to split a dataset into increasingly homogeneous subgroups having the greatest difference between the groups at each stage, was conducted with reference to previous literature [7,8].

Analyses

Logistic regression analyses were applied to establish the models. The maximum likelihood estimation was used as the method of coefficient estimation for each model.

Table 1 Coded Values

Coded value	Glasgow coma scale score	Systolic blood pressure (mmHg)	Respiratory rate (/min)	Age (years)	Injury Severity Score
4	13-15	> 89	10-29		< 16
3	9-12	76-89	> 29		16-24
2	6-8	50-75	6-9		25-40
1	4-5	1-49	1-5	≥ 55	41-65
0	< 4	No pulse	0	0-54	> 65

For model selection, Akaike's Information Criterion (AIC) [9], - 2log (maximum likelihood) +2 (number of adjusted parameters), was used. The model having the lower AIC is considered to be better fitting. The area under the receiver-operating characteristic curve (AUROCC), which distinguishes between survival and non-survival, and varies between 0.5 (= no discrimination) and 1 (= perfect discrimination), of each model was also measured.

The coefficients were simplified by rounding off after the decimal point or choosing 0.5 if it was nearer to the coefficients than 0 or 1.

The JMP 9.0 (SAS Institute Inc.) and SAS 9.1 (SAS Institute Inc.) software packages were used for statistical analyses.

The protocol of the present study was approved by the Ethics Committee of the National Center for Global Health and Medicine.

Results

Distributions of predictor variables and the proportion of survivors of each data set are shown in Table 2. The characteristics were substantially different between the Khon Kaen data and the JTDB data, in which both the derivation data and the validation data were similar.

The AIC and the AUROCC of each model are shown in Table 3. Over the set of models, the model with cISS, cAGE, cSBP, cGCS, and cRR as predictor variables showed the smallest AIC (1732), which was even smaller than the AIC for the model using ISS, RTS, and cAGE. Initially, six models that used only coded values and had lower AICs than that of the original TRISS model (1988) were selected for simplification. Then, the two models that had a higher AUROCC than the TRISS model and one model that does not require cISS were selected.

The estimated coefficients of the logistic regression models derived from the training data are shown with the original TRISS coefficients in Table 4. Each coefficient of cSBP, cGCS, and cRR on the TRISS line of the table was obtained from each coefficient of the RTS (0.7326, 0.9368 and 0.2908, respectively) multiplied by the coefficient of the RTS (0.8085) of the TRISS method using the 1990 version of AIS [2]. All estimated coefficients were significant.

The coefficients of cISS, cAGE, cSBP, and cGCS in Table 4 were rounded off after the decimal point, and the coefficient of cRR was regarded as 0.5.

The three developed models were as follows:

$$\text{logit (Ps)} = \text{intercept} + \beta = -9 + \text{cISS} - \text{cAGE} + \text{cSBP} + \text{cGCS} + \text{cRR}/2,$$

$$\text{logit (Ps)} = \text{intercept} + \beta = -7 + \text{cISS} - \text{cAGE} + \text{cSBP} + \text{cGCS},$$

$$\text{logit (Ps)} = \text{intercept} + \beta = -7 - \text{cAGE} + \text{cSBP} + \text{cGCS} + \text{cRR}/2,$$

$$\text{, where logit (Ps)} = \log(\text{Ps}/1 - \text{Ps})$$

Table 2 Distribution of Variables

		Derivation Data	Validation Data	Khon Kaen Data
Number		5113	5097	6407
cAGE	0	58.0%	58.5%	87.6%
	1	42.0%	41.5%	12.4%
RTS		7.8 [6.9, 7.8]	7.8 [6.9, 7.8]	7.8 [7.8, 7.8]
cSBP	4	85.0%	85.3%	95.9%
	3	3.2%	3.4%	1.6%
	2	2.6%	2.6%	1.1%
	1	1.3%	1.1%	0.2%
	0	7.9%	7.6%	1.2%
cGCS	4	72.4%	73.4%	89.4%
	3	7.5%	7.0%	3.0%
	2	6.1%	5.9%	4.6%
	1	2.6%	2.6%	1.1%
	0	11.4%	11.1%	1.9%
cRR	4	76.0%	76.8%	92.1%
	3	15.0%	14.8%	0.2%
	2	0.4%	0.4%	0.02%
	1	0.2%	0.1%	0.2%
	0	8.4%	7.9%	7.5%
ISS		17.6 ± 14.2	17.4 ± 14.0	9.5 ± 10.1
cISS	4	51.1%	51.0%	83.2%
	3	21.2%	22.3%	6.9%
	2	20.4%	19.7%	7.4%
	1	5.3%	5.2%	2.3%
	0	2.0%	1.8%	0.2%
Survival		82.1%	83.1%	95.9%

cAGE: coded value of age, RTS: the Revised Trauma Score shown by median [IQR],

cBP: coded value of systolic blood pressure, cGCS: coded value of the Glasgow Coma Scale score,

cRR: coded value of respiratory rate, ISS: the Injury Severity Score shown by mean ± standard deviation,

cISS: coded value of the Injury Severity Score

Table 3 Akaike's Information Criterion (AIC) and Discriminant Abilities for Each Model

Predictor variables used for each regression model	AIC	AUROCC
ISS, RTS, cAGE (original TRISS)	1988	0.9627
ISS, RTS, cAGE	**1788**	**0.9637**
ISS, cAGE, cSBP, cGCS, cRR	**1791**	**0.9637**
cISS, cAGE, cSBP, cGCS, cRR	**1732**	**0.9648**
cISS, cAGE, cSBP, cGCS	**1748**	**0.9649**
cISS, cAGE, cGCS, cRR	**1819**	0.9609
cISS, cSBP, cGCS, cRR	**1846**	0.9561
cISS, cSBP, cGCS,	**1854**	0.9562
cAGE, cSBP, cGCS, cRR	**1987**	0.9503
cAGE, cSBP, cGCS	2000	0.9465
cISS, cAGE, cGCS	2001	0.9547
cISS, cAGE, cSBP, cRR	2017	0.9481
cISS, cAGE, cBP	2024	0.9433

AUROCC: The area under the receiver-operating characteristic curve,

cAGE: coded value of age, RTS: the Revised Trauma Score, cBP: coded value of systolic blood pressure,

cGCS: coded value of the Glasgow Coma Scale score, cRR: coded value of respiratory rate,

ISS: the Injury Severity Score, cISS: coded value of the Injury Severity Score

As for the intercept of each model, the nearest integer (-7 or -9) to $-\beta$, where actual survival proportions just crossed 50% in the derivation data set, namely logit (Ps = 0.5) = 0, was chosen (Table 5).

For all models, including the models with missing variables, the AUROCCs were greater than 0.95 (Table 6). The same results were also shown for the Japanese validation data.

The AUROCCs of each model, applied to the data of the Khon Kaen Trauma Center in Thailand, are also shown in Table 6. The two models with cISS, cAGE, cSBP, cGCS as predictor variables showed AUROCCs greater than 0.96, almost the same as that of the TRISS model. For the model without cISS, the AUROCC was even greater than 0.91.

Discussion

The TRISS [1,2] method is the most popular method of survival estimation. However, it is not a suitable tool for quick assessment of survival probability in the clinical setting, because it requires complicated calculations using the ISS, for which precise coding of the Abbreviated Injury Scale (AIS) [10] is required, and the RTS, which also has complex coefficients for cGCS, cSBP, and cRR. Therefore, we tried to simplify Ps prediction without a significant decrease in accuracy for clinical rather than for administrative uses. Without substantial loss in the AUROCC compared with the original TRISS, the present study showed that logit (Ps) can be obtained even with a marked simplification of variables and intercepts (Table 6), sufficient to enable its mental calculation. In any case where logit (Ps) is greater than 0, by easy mental calculation it provides for quick determination as to whether the Ps is greater than 0.5, which is considered the lower limit for decision making about unexpected trauma death.

In addition to a recent report [11], the present study also directly used cSBP, cGCS, and cRR as predictor variables instead of the RTS. The ISS was coded based on our recent paper [7], and predictive models using the cISS were successfully constructed. Some of these models showed even smaller AICs or larger AUROCCs than those of the models using the ISS (Table 3). An important benefit of using the cISS instead of the ISS is that we can determine the cISS even without the information of the third most severe AIS score, which is sometimes lacking in physicians' records, as shown in Table 7 which was constructed with reference to Copes et al. [7]. This shows that, by dividing all variables into categories with adequate intervals, it is possible to perform

Table 4 Coefficients of Logistic Regression Models

Models with predictor variables	Intercept	β(c)ISS	βRTS	βcAGE	βcGCS	βcBP	βcRR
Original TRISS	-0.4499	-0.0835	0.8085	-1.743	0.7574	0.5923	0.2351
ISS, RTS, cAGE	-1.7162* (0.279) [37.8]	-0.0675* (0.005) [181]	0.9301* (0.0368) [639]	-1.439* (0.137) [111]	*	*	*
ISS, cAGE, cSBP, cGCS, cRR	-1.8646 (0.340) [30.2]	-0.0678* (0.0050) [181]	*	-1.452* (0.137) [112]	0.846* (0.047) [328]	0.670* (0.077) [75.8]	0.346* (0.090) [14.9]
cISS, cAGE, cSBP, cGCS, cRR	-6.281* (0.335) [351]	**1.0**58* (0.070) [227]	*	**-1.4**04* (0.137) [104]	**0.7**77* (0.047) [267]	**0.7**18* (0.077) [87.5]	**0.3**70* (0.090) [17.0]
cISS, cAGE, cSBP, cGCS	-5.734* (0.283) [410]	**1.0**38* (0.069) [225]	*	**-1.3**48* (0.136) [98.8]	**0.8**41* (0.045) [345]	**0.8**89* (0.063) [202]	x
cAGE, cSBP, cGCS, cRR	-4.663* (0.357) [170]	x	*	**-1.3**28* (0.129) [105]	**1.0**25* (0.044) [540]	**0.8**43* (0.077) [122]	**0.3**49* (0.094) [13.7]

Bx: regression coefficients, *: $p < 0.001$, (standard error), [likelihood ratio chi-square value],
PVs: predictor variables, cAGE: coded value of age, RTS: the Revised Trauma Score,
cBP: coded value of systolic blood pressure, cGCS: coded value of the Glasgow Coma Scale score,
cRR: coded value of respiratory rate, ISS: the Injury Severity Score,
cISS: coded value of the Injury Severity Score

Table 5 β value and Actual Survival Percentage in the Derivation Data

β	cISS-cAGE+cSBP+cGCS+cRR/2 Survival (%)	cISS-cAGE+cSBP+cGCS Survival (%)	-cAGE+cSBP+cGCS+cRR/2 Survival (%)
-1	0.0	0.0	0.0
0	0.0	0.0	0.0
1	0.0	0.0	0.0
2	0.0	0.0	0.0
3	1.7	11.8	30.0
4	14.0	19.7	28.0
5	30.0	26.8	33.8
6	32.4	40.3	47.6
7	28.8	**51.5**	**66.5**
8	38.3	75.3	82.7
9	**58.3**	88.5	96.5
10	78.7	96.7	99.5
11	91.4	98.6	
12	96.1	99.9	
13	98.5		
14	99.9		

If only one variable cannot be obtained, then a zero value is given for the missing predictor variable in each equation.
Actual survivals just crossed 50% around the nearest integer value of β (7 or 9)
cAGE: coded value of age, cBP: coded value of systolic blood pressure, cGCS: coded value of the Glasgow Coma Scale score, cRR: coded value of respiratory rate, cISS: coded value of the Injury Severity Score

Table 6 Proposed Regression Models with Simplified Coefficients

Logit (Ps) of each model	AUROCC JTDB derivation data	AUROCC JTDB validation data	AUROCC Khon Kaen registry data
-9 + cISS - cAGE + cSBP + cGCS + cRR/2	0.9635	0.9640	0.9619
-7 + cISS - cAGE + cSBP + cGCS	0.9633	0.9622	0.9601
-7 + cAGE + cSBP + cGCS + cRR/2	0.9503	0.9524	0.9115

AUROCC: The area under the receiver-operating characteristic curve,
cAGE: coded value of age, cBP: coded value of systolic blood pressure,
cGCS: coded value of the Glasgow Coma Scale score, cRR: coded value of respiratory rate,
cISS: coded value of the Injury Severity Score

Table 7 Relationship between Coded ISS and Most Severe Abbreviated Injury Scale (AIS)

Coded ISS	ISS Interval	Most severe AIS/2nd most severe AIS Included
4	< 16	**3**
3	16-24	**4**
2	25-40	**5** or **4**/3
1	41-65	Two **5** or **5**/4
0	> 65	Two **5**/4 or Three **5** or **6**

ISS: the Injury Severity Score

valid coding in cases where only an approximate value, not the exact value of ISS, is known.

Moreover, it was also shown that even if the cISS is undetermined, Ps calculation is nevertheless possible using just the age and vital sign factors, with only a slight decline in the AUROCC. This means that it is possible to predict Ps with high accuracy even for initial assessment at emergency centers in cases of undetermined anatomical severity. If a quick reference chart of Ps like Table 8 is prepared and kept in the pocket of physicians with Tables 1 and 7, Ps can be predicted without a computer. It can be used for hospital triage during initial management in case of a large number of BT victims, especially in multiple traffic or railroad accidents.

In Japan, RR information is frequently deficient [5], but with the regression equation presented in this study, even without information on cRR, only a slight decline in AUROCC is seen. As shown in Table 4 cRR had the lowest chi-square value in each model. This indicates that, based on their experience, Japanese surgeons or emergency physicians appear to have realized that RR is a less important indicator for survival in BT patients. From the results of Table 6 RR also seems to be unimportant in Thailand, because the models without cRR showed only a slight decline in the AUROCC. The deficiency that most increases the AIC and reduces the AUROCC is cGCS (Table 3), which had the highest chi-square value in each model (Table 4). Thus, the level of consciousness is the most important factor at the time of survival prediction. The importance of information on consciousness level was also proven in a different way in our recent paper [12].

The present study had a few limitations that might have biased the results. Because of missing data related to survival and the predictors, the Ps calculation of the TRISS could be done in only 58% of 17,564 BT patients registered in the JTDB. Tohira et al. [13] pointed out that significant differences existed in age, RTS, and ISS between outcome-missing data and non-outcome-missing data, and that selection bias may exist in research outputs gained from the extracted data from the JTDB by excluding patients with missing outcomes and the TRISS predictors. Thus, it seems to be of great worth to validate the developed models with the Khon Kaen trauma registry data, which are substantially different from the JTDB data in age, RTS, and ISS. At present, the simplified models in this study have been validated only with the Japan Trauma Registry data and the Khon Kaen Trauma Registry data in Thailand. If the results of the present study can be verified with other data from around the world, especially from middle-income countries where traffic injuries are rapidly increasing [14], it will be of greater use internationally.

Conclusion

The proposed, simplified equations allow quick assessments of Ps by simple mental calculation, which should prove useful at Asian emergency centers overcrowded with traffic accident victims suffering from blunt trauma.

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Authors' contributions

AK made substantial contributions to conception, acquisition of JTDB data, analysis and interpretation of data. SN was involved in drafting the manuscript or revising it critically for important intellectual content. WC made substantial contributions to acquisition of data from the Khon Kaen Regional Hospital Trauma Registry. All authors read and approved the final manuscript.

Table 8 Probability of Survival (Ps) Chart

b1~3	< -3	-2.5	-2	-1.5	-1	-0.5	0	0.5	1	1.5	2	2.5	> 3
Ps	< 0.05	0.08	0.12	0.18	0.27	0.38	0.5	0.62	0.73	0.82	0.88	0.92	0.95

$Ps = 1/(1 + e^{-b1\sim3})$

b1 = - 9 + cISS - cAGE + cSBP + cGCS + cRR/2

b2 = - 7 + cISS - cAGE + cSBP + cGCS

b3 = - 7 - cAGE + cSBP + cGCS + cRR/2

Competing interests
The authors certify that none of the authors has any financial or other relationships that could lead to a conflict of interest.

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Modification of the Trauma and Injury Severity Score (TRISS) Method Provides Better Survival Prediction in Asian Blunt Trauma Victims

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Abstract

Background The objective of the present study was to identify logistic regression models with better survival prediction than the Trauma and Injury Severity Score (TRISS) method in assessing blunt trauma (BT) victims in Japan and Thailand. An additional aim was to demonstrate the feasibility of probability of survival (Ps) estimation without respiratory rate (RR) on admission, which is often missing or unreliable in Asian countries.

Methods We used BT patient data ($n = 15{,}524$) registered in the Japan Trauma Data Bank (JTDB, 2005–2008). We also extracted data on BT patients injured in the Khon Kaen District between January 2005 and December 2008 ($n = 6{,}411$) from the Khon Kaen Hospital Trauma Registry. For logistic regression analyses, we chose the Injury Severity Score (ISS), age year (AY), Glasgow Coma Scale (GCS) score, systolic blood pressure (SBP), RR, and their coded values (c) as explanatory variables, as well as the Revised Trauma Score (RTS). We estimated parameters by the method of maximum likelihood estimation, and utilized Akaike's Information Criterion (AIC), the area under the receiver operating characteristic curve (AUROCC), and accuracy for model comparison. A model having the lower AIC is considered to be the better model.

Results The AIC of the model using AY was lower than that of the model using the coded value for AY (cAY) (used by the TRISS method). The model using ISS, AY and cGCS, cSBP, and cRR instead of the RTS demonstrated the lowest AIC in both data groups. The same trend could be observed in the AUROCCs and the accuracies. In the Khon Kaen data, we found no additional reduction of the AIC in the model using the cRR variable compared to the model without cRR.

Conclusions For better prediction of Ps, the actual number of the AY should be used as an explanatory variable instead of the coded value (used by the TRISS method). The logistic regression model using the ISS, AY, and coded values of SBP, GCS, and RR estimates the best prediction. Information about RR seems to be unimportant for survival prediction in BT victims in Asian countries.

Introduction

The Trauma and Injury Severity Score (TRISS) [1, 2] is a standard method for estimating survival and is often used in evaluating the quality of trauma care. It provides the probability of survival (Ps) by the logistic regression model with the predictor variables of the Injury Severity Score (ISS) [3], Revised Trauma Score (RTS) [4], and categorized data (coded value) of age year (cAY). The formula is:

$$\text{logit}(\text{Ps}) = \text{Intercept} + \beta\text{ISS}^{*}\text{ISS} + \beta\text{RTS}^{*}\text{RTS} + \beta\text{cAY}^{*}\text{cAY}$$

logit is the link function of the logistic regression model and represents the natural logarithm of the odds of the probability (Ps) of a positive outcome (survival/death). The

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